



Neglected Tropical Diseases as Hidden Causes of Cardiovascular Disease

Citation

Moolani, Yasmin, Gene Bukhman, and Peter J. Hotez. 2012. Neglected tropical diseases as hidden causes of cardiovascular disease. PLoS Neglected Tropical Diseases 6(6): e1499.

Published Version

doi:10.1371/journal.pntd.0001499

Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:10436277>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

Neglected Tropical Diseases as Hidden Causes of Cardiovascular Disease

Yasmin Moolani^{1‡}, Gene Bukhman², Peter J. Hotez^{3*}

1 George Washington University School of Medicine and Health Sciences, Washington, District of Columbia, United States of America, **2** Harvard Medical School, Boston, Massachusetts, United States of America, **3** Sabin Vaccine Institute and Texas Children's Center for Vaccine Development, Department of Pediatrics (Section of Pediatric Tropical Medicine) and Molecular Virology & Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, Texas, United States of America

An important component of the burden of cardiovascular disease in low- and middle-income countries may be attributed to the neglected tropical diseases.

There is a growing awareness of the importance of chronic non-communicable diseases (CNCDs) in the world's low- and middle-income countries (LMICs). Beginning in the 1990s, Murray and Lopez predicted a doubling of death rates due to cardiovascular disease in developing countries by 2020 [1], while a substantial rise was also predicted by Leeder et al. [2]. Based on World Health Organization (WHO) predictions, 75% of the burden of cardiovascular disease is found in LMICs [3]. Alarming increases have also been noted for other CNCDs in LMICs including cancer, chronic respiratory diseases, and diabetes [4]. In September 2011, a report by the World Economic Forum and the Harvard School of Public Health estimated the global economic burden of CNCDs over the next two decades to be US\$47 trillion [5]. During this same month, the United Nations General Assembly held a high-level meeting to discuss prevention and control of CNCDs, including cardiovascular diseases, in LMICs [6]. These initiatives have focused on preventable risk factors attributable to lifestyle changes such as tobacco and alcohol use, prolonged unhealthy nutrition, and physical inactivity, which currently account for a high proportion of cardiovascular deaths in North America and Europe [4–6].

While there is no question that obesity, tobacco, and alcohol represent major underlying conditions responsible for the rise of cardiovascular and other CNCDs in LMICs, they do not provide a complete picture. In March of 2011, Partners in Health and Harvard Medical School sponsored a conference entitled “The Long Tail of Global Health Equity: Tackling the Endemic Non-Communicable Diseases of the Bottom Billion” to examine in more detail some of the neglected causes of CNCDs, particularly those that are unique to the world's poorest people in LMICs. The conference highlighted important risk

factors apart from the lifestyle changes linked to CNCDs in high-income countries [7]. Specifically with respect to neglected populations, an important component of cardiovascular disease may be attributable to neglected tropical diseases (NTDs) and other infections of poverty. For example, the Heart of Soweto Study from South Africa identified rheumatic heart disease, tuberculosis, and HIV as significant contributors to heart disease and more common than coronary artery disease. Even in the urbanized region of Soweto where there is a high prevalence of vascular risk factors, non-ischemic etiologies are still the dominant cause of heart failure [8,9].

On a global level, the contribution of infections of poverty to heart disease can be seen in analyzing the Global Burden of Disease estimates from the WHO. According to this data, approximately 8.8% of the disability-adjusted life years (DALYs) of LMICs may be attributable to cardiovascular disease [3]. Almost one-half of this cardiovascular disease burden is attributable to ischemic heart disease, more than one-third to cerebrovascular disease, and the remainder to hypertensive and inflammatory causes, as well as rheumatic heart disease (Figure 1). A detailed analysis of these conditions suggests that NTDs and other neglected

infections may account for a significant component of each of these cardiovascular disease categories (Table 1).

Protozoan NTDs: American and African Trypanosomiasis

Approximately 10 million people are infected with *Trypanosoma cruzi*, the etiologic agent of Chagas disease (American trypanosomiasis), of whom up to 30% will develop Chagasic cardiomyopathy associated with heart failure, arrhythmias, and mural thrombi causing pulmonary and systemic emboli and sudden death [10–14]. Chronic heart failure is thought to be due to the persistence of trypanosome amastigotes in the heart, leading to a cascade of tissue destruction, myocarditis, fibrosis, and ultimately ventricular dilation [12]. Arrhythmias are similarly caused by fibrosis. The arrhythmias then predispose to various forms of emboli, and Chagas disease has been linked to ischemia and cerebrovascular disease and even stroke [13,14]. Thus, roughly 2–3 million people at any given time may be affected by Chagas cardiomyopathy, which can present either as ischemic or inflammatory heart disease or with mixed features of both [12–14]. While 99% of the DALYs associated with Chagas disease have been

Citation: Moolani Y, Bukhman G, Hotez PJ (2012) Neglected Tropical Diseases as Hidden Causes of Cardiovascular Disease. PLoS Negl Trop Dis 6(6): e1499. doi:10.1371/journal.pntd.0001499

Published: June 26, 2012

Copyright: © 2012 Moolani et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors received no funding for this work.

Competing Interests: Dr. Peter Hotez is principal investigator on a vaccine in development against Chagas disease.

* E-mail: hotez@bcm.edu

‡ **Current address:** Baylor College of Medicine, Houston, Texas, United States of America

Yasmin Moolani, MD, recently graduated from medical school at George Washington University and started Internal Medicine residency training at Baylor College of Medicine; Gene Bukhman, MD, PhD, is Assistant Professor of Medicine, Assistant Professor of Global Health and Social Medicine, and Director of the Program in Global Non-Communicable Disease and Social Change at Harvard Medical School; Peter Hotez, MD, PhD, is Co-Editor-in-Chief of *PLOS Neglected Tropical Diseases*, Texas Children's Hospital Endowed Chair of Tropical Pediatrics, Professor of Pediatrics and Molecular Virology & Microbiology, and Dean of the National School of Tropical Medicine, Baylor College of Medicine.

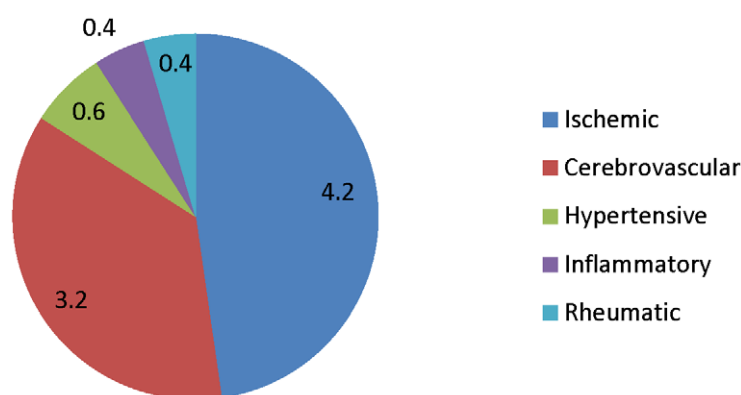


Figure 1. Distribution of DALYs attributed to cardiovascular disease among low- and middle-income countries (LMICs). Data obtained from WHO 2008 Global Burden of Disease estimates [3].

doi:10.1371/journal.pntd.0001499.g001

traditionally attributed to LMICs in the Americas, the “globalization” of Chagas disease from emigration is now recognized as a factor in a previously hidden burden of heart disease in the United States and Europe, especially Spain [15]. Globally, Chagas disease, therefore, accounts for a significant burden of ischemic and inflammatory heart disease in LMICs of the Americas and now accounts for an as yet undefined burden in some high-income

countries as well. Similarly, human African trypanosomiasis (HAT) can be associated with myocarditis and pericarditis, especially in the acute stages of the illness when the trypomastigote stages of the parasite spread through the blood and lymphatics to cause endarteritis [16]. On electrocardiography repolarization changes, prolonged QT intervals and low voltage can be seen in infected individuals [17]. About 50,000 to 70,000 people in

sub-Saharan Africa are thought to be infected with *Trypanosoma brucei*, with an annual incidence of approximately 17,000, and of infected patients 70% develop the above mentioned electrocardiographic changes [17,18].

Helminthic NTDs: Endomyocardial Fibrosis, Schistosomiasis, and Hookworm Infection

Endomyocardial fibrosis (EMF) causing restrictive cardiomyopathy is most prevalent in tropical and subtropical regions in the world. In endemic areas of sub-Saharan Africa, the prevalence of EMF reaches close to 20% and affects mostly children and young adults [19,20]. EMF is currently the fourth leading cause of heart disease in Nigeria, Africa’s most populous country [21,22]. EMF is also associated with pericarditis, arrhythmias, and mural thrombi [22,23]. The etiology of tropical EMF remains unclear; however, a number of factors and helminthic parasites have been implicated in its pathogenesis, particularly because its occurrence has been linked to eosinophilia and hypereosinophilia [22,24]. For that reason, endemic

Table 1. Estimated Prevalence of Cardiovascular Disease Caused by Neglected Tropical Diseases and Neglected Infections of Poverty.

NTD	Type of Cardiovascular Disease ^a	Estimated Number of People with the Infection	Number of Cases of Heart Disease or Related Conditions	References
Chagas disease	Ischemic, cerebrovascular, and inflammatory	10 million	2–3 million	[10–14]
HAT	Inflammatory	50,000–70,000 in sub-Saharan Africa	Not determined	[16–18]
Toxoplasmosis	Inflammatory	Up to 77% seroprevalence worldwide	19% of AIDS cardiomyopathy associated with acute myocarditis	[50,67,68]
EMF	Inflammatory	12 million	All	[23,58]
Schistosomiasis	Inflammatory (cardiomyopathy)	200 million	>270,000 with pulmonary hypertension	[28–34]
Hookworm	Inflammatory (CHF)	600 million	Not determined	[35–37,69]
Syphilis	Inflammatory	12 million	Untreated, 10% develop late cardiovascular complications	[40,41,70]
Tuberculosis	Inflammatory	2 billion (>10 million coinfecting with HIV)	1%–2% of people with pulmonary TB develop TB pericarditis	[46,48,71]
HIV	Inflammatory (pericarditis, cardiomyopathy)	34 million people worldwide with HIV and AIDS	Pericarditis: 19%–32% of asymptomatic people with AIDS not on HAART; Cardiomyopathy: 15%–57% of symptomatic and asymptomatic people with AIDS not on HAART	[49,50]
Dengue	Inflammatory	50–100 million cases annually	Myocardial dysfunction in 6.7% with DF, 13.8% with DHF, 36% with DSS	[54–56,72,73]
Rheumatic heart disease	Ischemic, cerebrovascular, rheumatic	RF: Up to 206/100,000 in developing world	RHD: Up to 18.6/100,000 in developing world	[51,52,74]

^aBased on WHO Global Burden of Disease categories.

NTD, neglected tropical disease; HAT, human African trypanosomiasis; AIDS, acquired immune deficiency syndrome; EMF, endomyocardial fibrosis; CHF, congestive heart failure; HIV, human immunodeficiency virus; TB, tuberculosis; HAART, highly active antiretroviral therapy; DF, dengue fever; DHF, dengue hemorrhagic fever without shock; DSS, dengue shock syndrome; RF, rheumatic fever; RHD, rheumatic heart disease.

doi:10.1371/journal.pntd.0001499.t001

filarial infections such as those caused by *Loa loa* and *Onchocerca volvulus* are among the leading candidate infections linked to this condition [22,25–27]. Two other helminths, *Schistosoma mansoni* and *Schistosoma japonicum*, cause chronic hepatosplenic schistosomiasis, an important cause of pulmonary hypertension and cor pulmonale. These pathologies occur in response to parasite egg deposition, hepatosplenic fibrosis, and portal hypertension [28–31]. Lapa et al. calculate that an estimated 200 million people worldwide are infected with any *Schistosoma* species, of whom 4%–8% develop hepatosplenic disease, and greater than 270,000 will go on to develop pulmonary artery hypertension [32]. However, more recently, King et al. suggest that previous estimates have been underestimating the true impact, and the prevalence of schistosomiasis-related disease is closer to 400–600 million worldwide [33]. Based on even the most conservative estimates, schistosomiasis may rank among the most prevalent causes of pulmonary hypertension worldwide [32,34]. Finally, among helminths causing cardiovascular disease, hookworm infection is a leading cause of iron deficiency anemia in LMICs [35]. Recent systematic reviews confirm strong links between hookworm infection and anemia among children and both pregnant and non-pregnant adults [36,37]. In Africa and Brazil, hookworm and *S. mansoni* schistosomiasis were shown to be synergistic [38]. Severe anemia is an important co-factor in congestive heart failure, although the contribution of hookworm disease and anemia to this condition is unknown.

Bacterial and Viral NTDs and Neglected Bacterial Infections

In their first ever report on NTDs in 2010, the WHO classified the endemic treponematoses, including *Treponema pallidum* (the cause of syphilis), as NTDs [39]. Late cardiovascular complications of syphilis, affecting 10% of untreated cases, cause obliterative endarteritis leading to syphilitic aortitis. The complications of syphilitic aortitis are coronary artery disease, valvular disease, and left ventricular volume overload hypertrophy [40]. A recent study in India assessing the prevalence of syphilitic aortitis in non-atherosclerotic aortic disease found 23% of aortic disease to be due to syphilis [41]. Tertiary syphilis can also, less commonly, cause gummatous myocarditis [42]. Of note, however, cardiovascular syphilis is considered a rare disease in developed countries [43]. A more ubiquitous bacteria, *Mycobacterium*

tuberculosis, leads to another cardiac manifestation, tuberculous pericarditis. Among patients with pulmonary tuberculosis, 1% to 2% develop tuberculous pericarditis. The various manifestations can include myopericarditis, pericardial constriction, pericardial effusion, and effusive-constrictive pericarditis [31]. In sub-Saharan Africa, 70% to 90% of large pericardial effusions and 10% of cases of congestive heart failure are caused by *M. tuberculosis* [31,44,45]. While the vast majority of cases of tuberculosis occur in developing countries, it is also seen in immigrant populations of developed countries, and thus the prevalence of tuberculous pericarditis reflects this distribution [46,47]. The disease is frequently diagnosed in HIV-positive patients, and when it is, it carries a mortality rate of 40% in 6 months compared to 17% in those without co-morbid HIV infection [48]. This form of pericarditis is associated with significant morbidity and mortality due to the effusions and constriction that occur despite appropriate medical therapy [48]. In the absence of *M. tuberculosis*, untreated HIV can still cause pericarditis as well as other forms of cardiovascular disease, including pulmonary hypertension and cardiomyopathy [49]. In Africa, toxoplasmosis and cryptococcosis are also important opportunistic infections associated with cardiomyopathy [50]. Finally, 80% of rheumatic heart disease associated with group A streptococcal infection occurs in LMICs [51]. The WHO data depicted in Figure 2 demonstrate the skewed burden weighted toward LMICs of the world, specifically in the Middle East and Asia, where substantially higher disease burdens (as measured in DALYs) exist [3]. These projections likely even underestimate the true burden of disease based on recent evidence [51]. The weighted burden toward LMICs is a relatively new phenomenon. Prior to the 1970s, rheumatic fever was an important cause of morbidity in developed countries; however, in the 1970s and 1980s, the prevalence of rheumatic fever began to decrease, while the rates in developing countries are an ongoing challenge and contribute significantly to the burden of disease [52]. The inequity between the wealthy and the poor can be seen even in high-income countries today where rheumatic heart disease disproportionately affects people living in poverty and indigenous populations [51,53]. Without adequate treatment, the mitral valve abnormalities characteristic of rheumatic heart disease predispose patients to other cardiac pathologies such as infectious endocarditis [8], thus making

rheumatic heart disease a contributing factor to both ischemic and cerebrovascular disease. Among the viral NTDs, most notably dengue fever has been associated with systolic and diastolic cardiac impairments [54], as well as myocarditis [55,56].

Policy Recommendations

We lack adequate data to determine the true extent of human cardiovascular disease that results from NTDs and other neglected infections of poverty. It also remains unclear how much of the world's ischemic heart disease and cerebrovascular disease, which account for most of the disease burden, may be due to neglected causes. There is an urgent need to understand the contribution of neglected diseases to heart disease in LMICs in order to design appropriate intervention strategies. This has been highlighted by others in the field who also acknowledge the presence of unique risk factors and heart pathologies in LMICs [8,11,20,31,57,58]. Towards that goal, stepped up measures for some of the neglected parasitic diseases might include increased screening for Chagas disease in the Americas (including the United States), Europe, and elsewhere using antibody-based testing now available [59], Doppler testing for pulmonary hypertension that results from schistosomiasis in Africa, and investigations into the etiology of EMF, especially tropical EMF linked to eosinophilia. Similarly, the extent to which bacterial infections such as syphilis, tuberculous pericarditis, and rheumatic heart disease (RHD) contribute to cardiovascular disease in LMICs remains unclear and requires improved diagnostic capabilities and testing. For RHD in particular, echocardiographic screening in school-aged populations is recognized as an important method of identifying subclinical rheumatic heart disease in the early stages prior to the progression to heart failure [53]. Such diagnostics and testing requires improved health systems in the developing world. Bukhman and Kidder have outlined novel methods of integrating services for RHD and heart failure into existing health systems in LMICs [60,61]. This can be expanded upon and tailored to specific regions.

There also remains a dearth of adequate control tools, that is, new drugs or vaccines for the neglected causes of human cardiovascular disease in LMICs. For instance, benznidazole and nifurtimox, the currently available drugs for treating Chagasic cardiomyopathy, require long treatment courses, and exhibit high levels

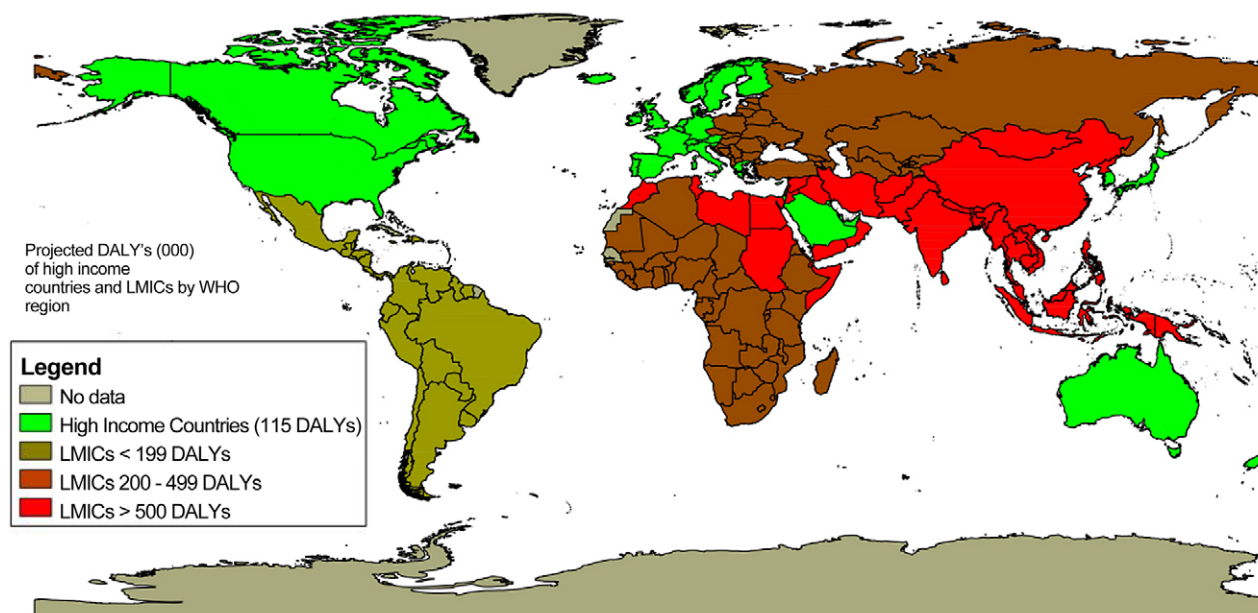


Figure 2. Distribution of DALYs attributed to rheumatic heart disease among low- and middle-income countries (LMICs). Rheumatic heart disease disproportionately affects LMICs. WHO Regions include Africa, the Americas, Eastern Mediterranean, Europe, South-East Asia, and Western Pacific (see Table S1 for list of countries in each region). The regions with the highest DALYs, greater than 500,000, include LMICs of Eastern Mediterranean (577,000), of South-East Asia (2,407,000), and of Western Pacific (1,095,000). DALYs attributed to rheumatic heart disease in LMICs of Africa amount to 317,000 and in LMICs of the Americas total 101,000 [3]. Map created using qGIS version 1.6.0 Capiapo.
doi:10.1371/journal.pntd.0001499.g002

of toxicities [62]. Their efficacy in achieving parasitologic cure is also in doubt and complicated by the absence of adequate biomarkers for assessing either progression of disease or clinical outcomes [63,64]. As an alternative intervention, efforts are in progress to develop and test therapeutic vaccines for Chagas disease [64]. Without a clear etiology, interventions for EMF beyond palliative surgeries for restrictive cardiomyopathy will be difficult to develop and test, while for schistosomiasis and hookworm there are needs to greatly expand coverage for annual mass drug administration using currently available anthelmintic drugs, as well as develop new anthelmintic vaccines to prevent anemia and heart disease, and forestall drug resistance [38]. For neglected bacterial infections, there is a need to accelerate new vaccines for tuberculosis [65,66] and

RHD [57] now in different stages of development, while the incidence of syphilis-associated heart disease may be reduced through expanded drug coverage.

Finally, as identified by Commerford and Mayosi, when the etiology and control mechanisms are known, research should include identifying social determinants that prevent disease management. Social determinants such as health systems, attitudes, and perceptions of both patients and physicians and socioeconomic factors should all be explored and recognized as important aspects of cardiovascular disease control and variable between ethnic groups [8]. With all the information gathered, the cost of prevention and control can be compared to the burden cost of the various causes of cardiovascular disease in LMICs.

Together, these interventions will address significant neglected causes of cardiovascular disease burden especially prevalent in LMICs. The growing interest in cardiovascular disease in these resource-poor settings is necessary to ensuring the health of the working-age population. Careful analysis reveals the need to look beyond lifestyle risk factors of developed countries and appreciate the nuances of chronic disease in developing countries. In doing so, we will more effectively facilitate the economic advancement of low- and middle-income populations.

Supporting Information

Table S1 List of countries in WHO income-based regions.
(DOCX)

References

- Murray CJL, Lopez AD (1996) Annex tables. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: 553.
- Leeder S, Raymond S, Greenberg H (2004) A race against time. The challenge of cardiovascular diseases in developing economies. Available: http://www.earthinstitute.columbia.edu/news/2004/images/raceagainstime_FINAL_051104.pdf. Accessed 24 May 2012.
- World Health Organization (2011) Projections of mortality and burden of disease, 2004–2030; standard DALYs (3% discounting, age weights) - baseline scenario; 2008; WHO regions. Available: http://www.who.int/entity/healthinfo/global_burden_disease/DALY7_2008.xls. Accessed 25 May 2012.
- World Health Organization (2005) Preventing chronic disease: a vital assessment. Available: http://www.who.int/chp/chronic_disease_report/en/. Accessed 25 May 2012.
- Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, et al. (2011) The global economic burden of non-communicable diseases. Available: http://www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf. Accessed 25 May 2012.
- United Nations Web Services Section, Department of Public Information (2011) 2011 high level meeting on prevention and control of non-communicable diseases. Available: <http://www.un.org/en/ga/ncdmeeting2011/>. Accessed 25 May 2012.
- Partners In Health (2011) The long tail of global health equity: tackling the endemic non-communicable diseases of the bottom billion. Available: <http://www.pih.org/pages/harvardncd>.

8. Commerford P, Mayosi B (2006) An appropriate research agenda for heart disease in Africa. *Lancet* 367(9526): 1884–1886.
9. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, et al. (2008) Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet* 371: 915–922.
10. World Health Organization (2011) Chagas disease (American trypanosomiasis). Available: <http://www.who.int/mediacentre/factsheets/fs340/en/index.html>. Accessed 25 May 2012.
11. Yacoub S, Mocumbi AO, Yacoub MH (2008) Neglected tropical cardiomyopathies: I. Chagas disease. *Heart* 94(2): 244–248.
12. Benvenuti LA, Rogério A, Freitas HFG, Mansur AJ, Fiorelli A, et al. (2008) Chronic american trypanosomiasis: parasite persistence in endomyocardial biopsies is associated with high-grade myocarditis. *Ann Trop Med Parasitol* 102(6): 481–487.
13. Paixão LC, Ribeiro AL, Valacio RA, Teixeira AL (2009) Chagas disease: independent risk factor for stroke. *Stroke* 40(12): 3691–3694.
14. Sambiasi NV, Higuchi ML, Benvenuti LA (2010) Narrowed lumen of the right coronary artery in chronic chagasic patients is associated with ischemic lesions of segmental thinnings of ventricles. *Invest Clin* 51(4): 531–539. Available: <http://www.scielo.org.ve/pdf/ic/v51n4/art09.pdf>. Accessed 25 May 2012.
15. Schmunis GA, Yadon ZE (2010) Chagas disease: A Latin American health problem becoming a world health problem. *Acta Trop* 115(1–2): 14–21.
16. Barratt JLN, Harkness J, Marriott D, Ellis JT, Stark D (2010) Importance of nonenteric protozoan infections in immunocompromised people. *Clin Microbiol Rev* 23(4): 795–836.
17. Carod-Artal FJ (2010) Trypanosomiasis, cardiomyopathy and the risk of ischemic stroke. *Expert Rev Cardiovasc Ther* 8(5): 717–728.
18. Hotez PJ, Kamath A (2009) Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Negl Trop Dis* 3(8): e412. doi:10.1371/journal.pntd.0000412.
19. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH (2008) A population study of endomyocardial fibrosis in a rural area of mozambique. *N Engl J Med* 359(1): 43–49.
20. Mocumbi AO, Yacoub S, Yacoub MH (2008) Neglected tropical cardiomyopathies: II. Endomyocardial fibrosis. *Heart* 94(3): 384–390.
21. Sovari AA, Kocheil AG (2010) Endomyocardial fibrosis. (1/21). Available: <http://emedicine.medscape.com/article/154931-overview#a0199>. Accessed 25 May 2012.
22. Andy JJ, Ogunowo PO, Akpan NA, Odigwe CO, Ekanem IA, et al. (1998) Helminth associated hyper eosinophilia and tropical endomyocardial fibrosis (EMF) in Nigeria. *Acta Trop* 69(2): 127–140.
23. Franco-Paredes C, Roupheal N, Méndez J, Folch E, Rodríguez-Morales AJ, et al. (2007) Cardiac manifestations of parasitic infections part 3: pericardial and miscellaneous cardiopulmonary manifestations. *Clin Cardiol* 30(6): 277–280.
24. Berenguer A, Plancha E, Gil JM (2003) Right ventricular endomyocardial fibrosis and microfilarial infection. *Int J Cardiol* 87(2–3): 287–289.
25. Ive FA, Willis AJ, Ikeme AC, Brockington IF (1967) Endomyocardial fibrosis and filariasis. *Q J Med* 36(144): 495–516.
26. Nutman TB, Miller KD, Mulligan M, Ottesen EA (1986) Loa loa infection in temporary residents of endemic regions: recognition of a hyperresponsive syndrome with characteristic clinical manifestations. *J Infect Dis* 154(1): 10–18.
27. Bukhman G, Ziegler J, Parry E (2008) Endomyocardial fibrosis: still a mystery after 60 years. *PLoS Negl Trop Dis* 2(2): e97. doi: 10.1371/journal.pntd.0000097.
28. Cheever AW, Kamel IA, Elwi AM (1978) Schistosoma mansoni and S. haematobium infections in Egypt. III. extrahepatic pathology. *Am J Trop Med Hyg* 27(1 I): 55–75.
29. De Clewa R, Herman P, Pugliese V, Zilberstein B, Saad WA, et al. (2003) Prevalence of pulmonary hypertension in patients with hepatosplenic mansonic schistosomiasis - prospective study. *Hepato-gastroenterology* 50(54): 2028–2030.
30. Morris W, Knauer CM (1997) Cardiopulmonary manifestations of schistosomiasis. *Semin Respir Infect* 12(2): 159–170.
31. Mocumbi AOH, Ferreira MB (2010) Neglected cardiovascular diseases in Africa. Challenges and opportunities. *J Am Coll Cardiol* 55(7): 680–687.
32. Lapa M, Dias B, Jardim C, Fernandes CJC, Dourado PMM, et al. (2009) Cardiopulmonary manifestations of hepatosplenic schistosomiasis. *Circulation* 119(11): 1518–1523.
33. King CH (2010) Parasites and poverty: the case of schistosomiasis. *Acta Trop* 113(2): 95–104.
34. Van Der Werf MJ, De Vlas SJ, Brooker S, Looman CWN, Nagelkerke NJD, et al. (2003) Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Trop* 86(2–3): 125–139.
35. Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, et al. (2004) Hookworm infection. *N Engl J Med* 351(8): 799–807+841.
36. Brooker S, Hotez PJ, Bundy DAP (2008) Hookworm-related anaemia among pregnant women: a systematic review. *PLoS Negl Trop Dis* 2(9): 291. doi:10.1371/journal.pntd.0000291.
37. Smith JL, Brooker S (2010) Impact of hookworm infection and deworming on anaemia in non-pregnant populations: a systematic review. *Trop Med Int Health* 15(7): 776–795.
38. Hotez PJ, Bethony JM, Diemert DJ, Pearson M, Loukas A (2010) Developing vaccines to combat hookworm infection and intestinal schistosomiasis. *Nat Rev Microbiol* 8(11): 814–826.
39. World Health Organization (2010) First WHO report on neglected tropical diseases: working to overcome the global impact of neglected tropical diseases. Available http://www.who.int/neglected_diseases/2010report/en/. Accessed 25 May 2012.
40. World Health Organization (2001) Global prevalence and incidence of selected curable sexually transmitted infections: overview of estimates. Available: http://www.who.int/reproductivehealth/publications/rtis/HIV_AIDS_2001_2/en/index.html. Accessed 25 May 2012.
41. Vaideswar P (2010) Syphilitic aortitis: rearing of the ugly head. *Indian J Pathol Microbiol* 53(4): 624–627.
42. Leach W (1960) Case report: gummatous myocarditis. *Br Heart J* 22: 149–152.
43. Jackman JD Jr, Radolf JD (1989) Cardiovascular syphilis. *Am J Med* 87(4): 425–433.
44. Cegielski JP, Ramiya K, Lallinger GJ, Mtulia IA, Mbaga IM (1990) Pericardial disease and human immunodeficiency virus in Dar es Salaam, Tanzania. *Lancet* 335: 209–212.
45. Mayosi BM, Volmink JA, Commerford PJ (2007) Pericardial disease: an evidence-based approach to diagnosis and treatment. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. *Evidence-based cardiology*. Second edition. London: BMJ Books.
46. Larrieu AJ, Tyers GFO, Williams EH, Derrick JR (1980) Recent experience with tuberculous pericarditis. *Ann Thorac Surg* 29(5): 464–468.
47. Trautner BW, Darouiche RO (2001) Tuberculous pericarditis: optimal diagnosis and management. *Clin Infect Dis* 33(7): 954–961.
48. Mayosi BM, Wiysonge CS, Ntsheke M, Gumedze F, Volmink JA, et al. (2008) Mortality in patients treated for tuberculous pericarditis in sub-Saharan Africa. *S Afr Med J* 98(1): 36–40.
49. Ntsheke M, Mayosi BM (2009) Cardiac manifestations of HIV infection: an African perspective. *Nat Clin Pract Cardiovasc Med* 6(2): 120–127.
50. Magula NP, Mayosi BM (2003) Cardiac involvement in HIV-infected people living in africa: a review. *Cardiovasc J S Afr* 14(5): 231–237.
51. Carapetis JR, Steer AC, Mulholland EK, Weber M (2005) The global burden of group A streptococcal diseases. *Lancet Infect Dis* 5(11): 685–694.
52. Carapetis JR (2007) Rheumatic heart disease in developing countries. *N Engl J Med* 357(5): 439–441.
53. Marjion E, Ou P, Celermajor DS, Ferreira B, Mocumbi AO, et al. (2007) Prevalence of rheumatic heart disease detected by echocardiographic screening. *New Engl J Med* 357(5): 470–476.
54. Yacoub S, Griffiths A, Chau TTH, Simmons CP, Wills B, et al. (2011) Cardiac function in Vietnamese patients with different dengue severity grades. *Crit Care Med* 40(2): 477–483.
55. Lee IK, Lee WH, Liu JW, Yang KD (2010) Acute myocarditis in dengue hemorrhagic fever: A case report and review of cardiac complications in dengue-affected patients. *Int J Infect Dis* 14(10): e919–e922.
56. Salgado DM, Eltit JM, Mansfield K, Panqueba C, Castro D, et al. (2010) Heart and skeletal muscle are targets of dengue virus infection. *Pediatr Infect Dis J* 29(3): 238–242.
57. Carapetis JR, Zuhlke LJ (2011) Global research priorities in rheumatic fever and rheumatic heart disease. *Ann Pediatr Card* 4(1): 4–12.
58. Yacoub S, Kotit S, Mocumbi AO, Yacoub MH (2008) Neglected diseases in cardiology: a call for urgent action. *Nat Clin Pract Cardiovasc Med* 5(4): 176–177.
59. Centers for Disease Control and Prevention (2010) Chagas disease - resources for health professionals - diagnosis. Available: http://www.cdc.gov/parasites/chagas/health_professionals/dx.html. Accessed 25 May 2012.
60. Bukhman G, Kidder A (2008) Cardiovascular disease and global health equity: lessons from tuberculosis control then and now. *Am J Public Health* 98: 44–54.
61. Bukhman G, Kidder A, eds. (2010) *The Partners In Health guide to chronic care integration for endemic non-communicable diseases - Rwanda edition*. Partners In Health. Available: <http://www.pih.org/publications/entry/the-pih-guide-to-chronic-care-integration-for-endemic-ncd>. Accessed 25 May 2012.
62. Hotez PJ, Pecoul B (2010) “Manifesto” for advancing the control and elimination of neglected tropical diseases. *PLoS Negl Trop Dis* 4(5): e718. doi:10.1371/journal.pntd.0000718.
63. Lannes-Vieira J, de Araújo-Jorge TC, de Nazaré Correia Soeiro M, Gadelha P, Corrêa-Oliveira R (2010) The centennial of the discovery of chagas disease: facing the current challenges. *PLoS Negl Trop Dis* 4(6): e645. doi:10.1371/journal.pntd.0000645.
64. Hotez PJ, Dumonteil E, Heffernan MJ, Bottazzi ME. Innovation for the “bottom billion”: eliminating neglected tropical diseases in the Americas through mass drug administration and new vaccines for hookworm and Chagas disease. *Adv Exp Med Biol* In press.
65. Aeras Global TB Vaccine Foundation (2010) Aeras annual report 2011: answering the call for a TB free world. Available: <http://www.aeras.org/annualreport2010/>. Accessed 25 May 2012.
66. Kaufmann SHE (2000) Is the development of a new tuberculosis vaccine possible? *Nat Med* 6(9): 955–960.
67. Tenter AM, Heckerth AR, Weiss LM (2000) *Toxoplasma gondii*: from animals to humans. *Int J Parasitol* 30(12–13): 1217–1258.
68. Longo-Mbenza B, Seghers KV, Phuati M, Nkiabungu Bikangi F, Mubagwa K (1998) Heart involvement and HIV infection in African patients: determinants of survival. *Int J Cardiol* 64(1): 63–73.
69. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, et al. (2007) Control of neglected tropical diseases. *N Engl J Med* 357(10): 1018–1027.

70. Harrison LW (1956) The Oslo study of untreated syphilis, review and commentary. *Br J Vener Dis* 32(2): 70–78. doi:10.1136/sti.32.2.70.
71. World Health Organization (1999) The world health report 1999 - making a difference. Available: <http://www.who.int/whr/1999/cn/index.html>. Accessed 25 May 2012.
72. [No authors listed] (2000) TDR research on dengue: recommendations of a scientific working group. June 2000. *TDR News* (62): 3, 15.
73. Khongphatthanayothin A, Lertsapcharoen P, Supachokchaiwattana P, La-orkhun V, Khumtonvong A, et al. (2007) Myocardial depression in dengue hemorrhagic fever: prevalence and clinical description. *Pediatr Crit Care Med* 8(6): 524–529.
74. Eisenberg MJ (1993) Rheumatic heart disease in the developing world: prevalence, prevention, and control. *Eur Heart J* 14(1): 122–128.